# Combination therapy with warfarin plus clopidogrel improves outcomes in femoropopliteal bypass surgery patients

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***Background:*** **Patients having undergone femoropopliteal bypass surgery remain at significant risk of graft failure. Although antithrombotic therapy is of paramount importance in these patients, the effect of oral anticoagulation therapy (OAT) on outcomes remains unresolved. We performed a randomized, prospective study to assess the impact of OAT plus clopidogrel vs dual antiplatelet therapy on peripheral vascular and systemic cardiovascular outcomes in patients who had undergone femoropopliteal bypass surgery.**

***Methods:*** **Three hundred forty-one patients who had undergone femoropopliteal surgery were enrolled and randomized: 173 patients received clopidogrel 75 mg/d plus OAT with warfarin (C + OAT), and 168 patients received dual antiplatelet therapy with clopidogrel 75 mg/d plus aspirin 100 mg/d (C + acetylsalicylic acid [ASA]). Study end points were graft patency and the occurrence of severe peripheral arterial ischemia, and the incidence of bleeding episodes.**

***Results:*** **Follow-up ranged from 4 to 9 years. The graft patency rate and the freedom from severe peripheral arterial ischemia was significantly higher in C + OAT group than in C + ASA group ($P = .026$ and .044, respectively, Cox-Mantel test). The linearized incidence of minor bleeding complications was significantly higher in C + OAT group than in C + ASA group (2.85% patient-years vs 1.37% patient-years; $P = .03$). The incidence of major adverse cardiovascular events, including mortality, was found to be similar ($P = .34$) for both study groups.**

***Conclusions:*** **In patients who have undergone femoropopliteal vascular surgery, combination therapy with clopidogrel plus warfarin is more effective than dual antiplatelet therapy in increasing graft patency and in reducing severe peripheral ischemia. These improvements are obtained at the expenses of an increase in the rate of minor anticoagulation-related complications. (J Vasc Surg 2012;56:96-105.)**

Patients having undergone femoropopliteal bypass surgery remain at significant risk of graft failure, despite a careful surgical technique.[1-3] In the first year after operation, the incidence of graft occlusion is as high as 28% to 45% and the treatment with antithrombotic agents seems to impact favorably on postoperative results.[4-6] Moreover, in patients with peripheral arterial disease the risk of myocardial infarction, stroke, or death from cardiovascular causes is three times as high as for persons without peripheral arterial disease.[7,8] Many studies evaluated the efficacy of antiplatelet therapy in maintaining vascular patency in various categories of patients, and while the evidence for a benefit of antiplatelet therapy after prosthetic femoropopliteal bypass surgery is widely accepted, to date, the benefit for autogenous saphenous vein graft is not clearly demonstrated.[9-11] However, there is general agreement that antiplatelet therapy is of paramount importance in these patients to improve the results and to prevent atherosclerotic complications.[12]

The effect of long-term oral anticoagulation therapy (OAT) on early and long-term outcome after femoropopliteal arterial reconstruction remains unresolved.[13,14] Recently, the Warfarin Antiplatelet Vascular Evaluation (WAVE) randomized trial reported that the combination of an oral anticoagulant plus an antiplatelet drug was not more effective than antiplatelet therapy alone in preventing major cardiovascular events, and further, it was associated with an increased life-threatening risk of bleeding.[15] Other studies have demonstrated that in high-risk patients oral anticoagulant plus antiplatelet therapy appears to be more effective than antiplatelet-only therapy in reducing the risk of graft occlusion.[4,16,17]

Clopidogrel, an adenosine diphosphate receptor antagonist that inhibits platelet activation, has shown in clinical practice a favorable benefit/risk ratio in preventing cardiovascular events,[18] although there is no general agreement on its efficacy in stable patients and in long-term therapy.[19,20]

To date, no study has been carried out to determine the efficacy of combination therapy with oral anticoagulant and clopidogrel on peripheral vascular patients.

We have performed a randomized, prospective study with the aim of assessing the early and long-term impact of oral anticoagulant plus clopidogrel therapy vs dual antiplatelet (clopidogrel plus aspirin) therapy on peripheral vascular and on systemic cardiovascular outcomes in a

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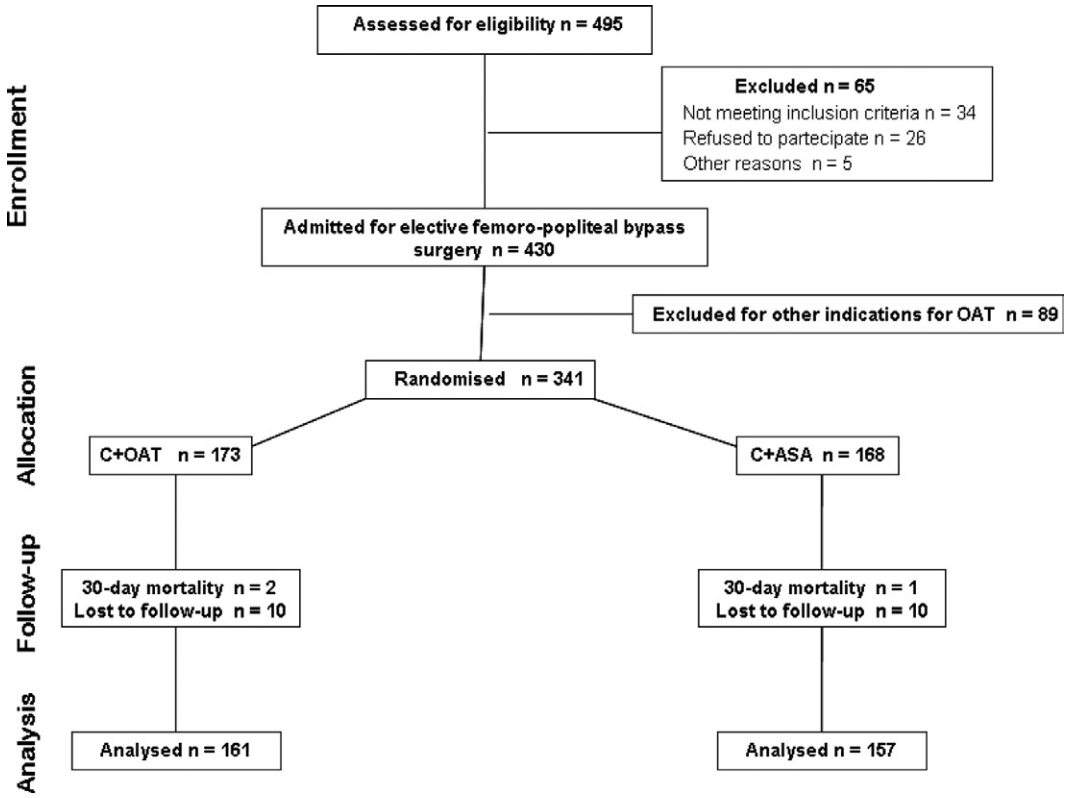


**Fig 1.** Consort diagram for the study flow. *C + ASA*, Clopidogrel plus acetylsalicylic acid therapy patients; *C + OAT*, clopidogrel plus oral anticoagulation therapy patients; *OAT*, oral anticoagulation therapy.

consecutive series of peripheral vascular patients who had undergone femoropopliteal bypass surgery.

## METHODS

**Study design.** The present study was an open-label randomized trial. It was conducted at two centers performing cardiovascular surgery in Italy, was approved by the ethics review boards of both participating institutions, and all patients provided written informed consent.

From January 2002 to December 2006, all patients with atherosclerotic lesions of the lower extremities and in need of femoropopliteal surgery were enrolled (Fig 1). Preoperatively, all patients underwent digital subtraction angiography (DSA) of abdominal aorta and lower extremities. Furthermore, an ultrasonic echo-Doppler scan of lower extremity arteries, abdominal aorta and iliac axis, and the ankle-brachial pressure index (ABPI) by Doppler method at rest were obtained in all enrolled patients.

Indication to femoropopliteal bypass surgery was objective evidence of peripheral arterial disease (occlusion or stenosis ≥75%) with intermittent claudication, ischemic pain at rest, nonhealing ulcers or focal gangrene, previous amputation, arterial revascularization, and the blue toe syndrome.

Patients were considered to be at high risk for graft failure, according to DSA evaluation, in the presence of poor arterial runoff, defined as occlusion of one of the tibial arteries or diffuse disease in both tibial arteries with multiple sites of >50% stenoses, in the presence of occlusion or diffuse disease of the peroneal artery, and/or redo femoropopliteal bypass grafting. Patients with only peroneal artery patency were not included in the study population, because they are not comparable to patients with at least one tibial artery patency, due to the relative importance of the peroneal artery on runoff bed.[21]

During the study period, 430 consecutive patients were admitted for elective femoropopliteal bypass surgery. Patients were excluded if there were other indications for OAT, atrial fibrillation or mechanical cardiac prosthesis (59 patients, 13.7%), they had active bleeding (eight patients, 1.9%), had a stroke within 6 months before enrollment (12 patients, 2.8%), or required dialysis (10 patients, 2.3%). A total of 341 patients met criteria for inclusion; randomization to the type of procedure was made after the patient was deemed eligible, and each patient was assigned to either group by the last digit of his or her hospital admission number. In total, 173 patients received clopidogrel 75 mg/d plus OAT with warfarin (C + OAT group), and 168 patients received dual antiplatelet therapy with clopidogrel 75 mg/d plus aspirin 100 mg/d (C + acetylsalicylic acid [ASA] group).

In the present study, we decided to use a low-intensity regimen of anticoagulation, maintaining the INR value between 2.0 and 2.5. By the light of medical literature tendency to use a low-medium intensity of anticoagulation (INR 1.5-3-0) in a variety of clinical settings, such as atrial fibrillation, mechanical cardiac prosthesis, and deep venous thrombosis prophylaxis,[22-24] we hypothesized that also in peripheral vascular patients, a low-medium intensity INR range will be effective and safer than standard INR range.

From the second postoperative day, all patients in both groups received enoxaparin (1 mg/kg/d), which was withdrawn in C + OAT patients when the target INR was reached and at the fourth postoperative day for C + ASA patients. Both therapeutic regimens (C + OAT and C + ASA) were started on the second postoperative day.

Preoperatively, all patients underwent preoperative peripheral angiography of abdominal aorta and lower extremities. Furthermore, an ultrasonic echo-Doppler scan of lower extremity arteries, abdominal aorta and iliac axis, and the ABPI by Doppler method at rest were obtained in all enrolled patients.

The arterial bypass grafting was done with either general balanced or epidural anesthesia. The bypass grafts were constructed in all enrolled patients with knitted gelatin- or collagen-coated Dacron prosthesis (Gelsoft; Vascutek, Inchinnan, Scotland, UK, or Intergard; Maquet Cardiovascular, Restatt, Germany) for above-knee (AK) site of distal anastomosis and with internal saphenous vein, in a reversed fashion, for below-knee (BK) outflow site. All patients underwent systemic anticoagulation with heparin (1 mg/kg) intravenously before arterial occlusion, maintaining an activated clotting time above 250 seconds. The bypass grafts were constructed with standard surgical techniques, and arteriography was done at completion of the bypass grafting procedure to assess its technical adequacy. Anticoagulation therapy with heparin was not reversed at the completion of the procedure. We decided to include in the present study only prosthetic AK and autogenous BK femoropopliteal bypass to obtain a strong uniformity of population, so that we will be able to maintain a strict adherence to study protocol during the entire enrollment period at the two study centers, avoiding confusion. Moreover, while for BK outflow site there is no doubt that the saphenous vein represents the first choice,[2] many studies have addressed the good results with AK prosthetic Dacron bypass as a simple and straightforward procedure.[25,26]

**Study end points and definitions.** Coprimary study end points were graft patency, defined as an ABPI $\geq 0.9$ with a duplex ultrasound graft scan examination that showed velocities of more than 30 cm/s and $<150$ cm/s, and the absence of severe peripheral arterial ischemia threatening the viability of the limb and leading to amputation. Primary patency rate, primary-assisted patency rate, and secondary patency rate were defined according to the Sarac study.[16] Primary and primary-assisted graft patency rates were included in the analysis, while secondary graft patency was considered as graft failure: the incidence of life-threatening, moderate, or minor bleeding episodes. Life-threatening bleeding was defined as fatal or intracranial bleeding or bleeding requiring hospitalization and transfusion of more than 2 units of blood or fresh-frozen plasma. Moderate bleeding was defined as intraocular hemorrhage or as bleeding requiring hospitalization and transfusion of $<2$ units of blood or blood products. All other bleeding, not requiring hospitalization and/or transfusion, was classified as minor.

Secondary end point was the occurrence of any major adverse cardiovascular event (MACE), such as myocardial infarction, stroke, severe ischemia of the coronary arteries leading to urgent intervention, or death from cardiovascular causes. Death from cardiovascular causes was defined as any death for which there was no clearly documented noncardiovascular cause. Myocardial infarction was defined as the presence of diagnostic electrocardiographic changes and/or elevation of the level of serum creatine kinase MB fraction, or serum troponin ($3 \times$ normal value). Stroke, both ischemic or hemorrhagic, was defined as a new focal neurologic deficit lasting more than 24 hours and documented by a computed tomographic or magnetic resonance imaging scan. Severe coronary ischemia was defined as unstable angina with electrocardiographic changes requiring hospitalization and coronary revascularization.

**Follow-up.** Patients were followed up for a minimum of 4 years and for a maximum of 9 years. Follow-up data, at 30 days if a patient had been discharged from the hospital and every 4 months thereafter, were obtained directly from the patients in the outpatient clinic and/or their family physician by telephone call or by written questionnaire. Information on events, other hospitalizations, and adherence to the assigned treatment regimen was achieved. INR values were checked every month or more frequently, as appropriate. All patients underwent ultrasonic echo-Doppler scan evaluation, including rest ABPI, every 6 months.

**Variables.** The preoperative variables tested for their association with outcome included age, gender, urgent operation, ABPI, high risk for graft failure, AK synthetic graft, BK vein graft, left ventricular ejection fraction, New York Heart Association (NYHA) class, hepatic dysfunction, defined as abnormal prothrombin activity ($<65\%$) and serum transaminases level ($\times$ two normal value), serum creatinine level, presence of diabetes, coexistent coronary artery disease, previous myocardial infarction, and previous cerebrovascular accident.

**Statistical analysis.** All variables are presented as mean and standard deviation of the mean. Student t test for unpaired data, $\chi^2$, or Fisher exact test were used, as appropriate. Two-tailed tests of significance are reported, and $P$ values less than .05 were considered statistically significant.

Intention-to-treat analyses provided information about events from the time of randomization. If more than one end point occurred within the follow-up period, only the first event was considered.

Patients could experience more than one end point if they suffered different discrete end points. If more than one end point occurred within the follow-up period, then the

**Table I.** Demographics and comorbidities

| | *C + OAT n = 173* | *C + ASA n = 168* | P *value*[a] |
|---|---|---|---|
| Mean age (y, mean ± SD) | 68.4 ± 12.4 | 66.2 ± 14.2 | .14 |
| Sex (male), n (%) | 116 (67.0) | 122 (72.6) | .15 |
| Hypertension, n (%) | 135 (78.1) | 140 (83.3) | .17 |
| Coronary artery disease, n (%) | 110 (63.6) | 97 (57.7) | .25 |
| Diabetes mellitus, n (%) | 78 (45.1) | 84 (50.0) | .35 |
| COPD, n (%) | 48 (27.7) | 53 (31.5) | .42 |
| Currently smoking, n (%) | 38 (18.5) | 45 (26.8) | .25 |
| Renal insufficiency (Cr >1.7), n (%) | 53 (30.6) | 40 (23.8) | .22 |
| High risk for graft failure, n (%) | 41 (23.7) | 37 (22.0) | .81 |

*C + ASA*, Patients who underwent therapy with aspirin and clopidogrel; *C + OAT*, patients who underwent therapy with warfarin and clopidogrel; *COPD*, chronic obstructive pulmonary disease; *Cr*, creatinine, expressed in mg/dL.
[a]Significant <.05 with $\chi^2$ test.

more severe end point only was counted. Graft patency, limb salvage rates, and incidence of MACEs, including survival, were compared with the Kaplan-Meier analysis, using the long-rank test (Cox-Mantel) to ascertain differences between groups. The rate of bleeding was calculated with linearized rates expressed as events/100 patient-years of follow-up and reported with a 95% confidence interval (CI). The likelihood-ratio test was used to compare the linearized rates between the two study groups.

Logistic regression analysis and the Cox proportional hazards regression model were used to analyze the factors associated to primary end points (graft patency rate and bleeding episode incidence). Linearity assumption for continuous variables was assessed by checking the significance of the transformed variable added to the model. Transforming was achieved by taking the natural logarithm and the square of the variable. Proportional hazard assumption was met in all models. When the linearity of the variable age was not met, the final Cox model included both the linear and the square term of this variable.[27] Among patients receiving oral anticoagulation, the time in the therapeutic range was calculated by the linear-interpolation method described by Rosendaal.[28]

In a systematic review of antiplatelet therapy randomized controlled trials,[4] a median incidence of 30% of graft occlusion was reported, at a median of 2.0 years after randomization. Therefore, our study enrolled a total sample >340 patients to observe a 20% reduction, ie, 24% incidence of long-term graft failure, with a statistical power >80% (1-β error level) to detect a probability of <.05 (α error level). All data were analyzed using STATISTICA 6.0 (StatSoft Inc, Tulsa, Okla).

## RESULTS

**Early and 30-day outcome.** There were no differences between the two groups studied in age, sex, and comorbidities (Table I). Operative data and perioperative and 30-day outcomes are shown in Table II. Fourteen patients (0.4%) necessitated a surgical perioperative revision for significant bleeding: eight on C + OAT and six on C + ASA ($P = .8$). Early reintervention for primary-assisted patency was required in eight patients, four in each study group (2.3% in C + OAT group and 2.4% in C + ASA group; $P = .8$). In all cases, after intraprocedural angiography to detect the site (inflow and/or outflow) to treat, an angioplasty was performed trimming the ends of grafts to form an enlarged lumen. Only one perioperative death occurred, in the C + OAT group (0.6%; $P = .5$ vs C + ASA group), and the overall 30-day mortality was three patients (0.88%, 2 in C + OAT vs 1 in C + ASA patients; $P = .5$). The incidence of all 30-day complications, either peripheral-arterial-related or MACEs, the length of hospital stay (LOS), and the number of packed red blood cells transfused were not different in either group (Table II). The 30-day primary or primary-assisted graft patency was higher, although not statistically significant, for the C + OAT group than for the C + ASA group (98.2% vs 93.7%; $P = .07$, odds ratio [OR] = 0.27, 95% CI = 1.1-6.5), while the median ABPI was similar in both groups (0.93 ± 0.14 in C + OAT vs 0.91 ± 0.16; $P = .3$).

At multivariate analysis, the only causes influencing the coprimary study end points were urgent operation ($P = .01$, exp (B) = 0.17, 95% CI = 0.04-0.67), high risk for graft occlusion ($P = .002$, exp (B) = 0.23, 95% CI = 0.09-0.57), and hepatic dysfunction ($P = .006$, exp (B) = 1.06, 95% CI = 1.01-1.61).

**Long-term outcome.** Mean duration of follow-up was 6.39 ± 1.6 years (median, 6.6 years) and included 161 patients for the C + OAT group and 157 patients for the C + ASA group: 94.1% and 93.4%, respectively. Among patients receiving oral anticoagulation, the mean INR was 2.2; of interest is that 86.0% of the time, the INR values were in the therapeutic range (2.0-2.5), while in 9.2% of the time, they were below 2.0, and finally 4.8% of the time, they were above 2.5.[28]

The linearized rate of bleeding at follow-up is reported in Table III. The overall incidence rates of life-threatening or moderate anticoagulation therapy-related complications (considered together because either required transfusion and/or hospitalization) were similar in the two study groups (1.78% patient-years in the C + OAT group and 1.62% patient-years in the C + ASA group; $P = .7$), while

**Table II.** Operative data and early (perioperative and <30 days) morbidity and mortality rates

| | *C + OAT n = 173* | *C + ASA n = 168* | P *value* |
|---|---|---|---|
| Mortality, n (%) | 2 (1.2) | 1 (0.6) | .50 |
| Myocardial infarction, n | 1 | 1 | |
| Respiratory (pneumonia), n | 1 | 0 | |
| Hemorrhagic, n (%) | 10 (5.8) | 11 (6.5) | .94 |
| Wound hematoma n | 5 | 3 | .37 |
| Gastrointestinal, n | 2 | 3 | .48 |
| Central nervous system, n | — | 1 | .49 |
| Genitourinary, n | 3 | 4 | .48 |
| Bypass graft data | | | |
| Femoropopliteal AK, n (%) | 110 (63.6) | 111 (70.2) | .26 |
| Femoropopliteal BK, n (%) | 63 (36.4) | 47 (29.7) | .26 |
| Graft failure, n (%) | 4 (2.3) | 10 (5.9) | .07 |
| In high risk patients, n (%) | 2 (50.0) | 6 (60.0) | .10 |
| MACEs, n (%) | 3 (1.7) | 5 (2.9) | .34 |
| LOS days, mean ± SD | 6.3 ± 1.9 | 6.5 ± 2.2 | .38 |
| Packed red blood cells units, mean ± SD | 0.4 ± 0.7 | 0.5 ± 0.6 | .17 |

*AK*, Above-knee; *BK*, below-knee; *C + ASA*, patients who underwent therapy with aspirin and clopidogrel; *C + OAT*, patients who underwent therapy with warfarin and clopidogrel; *LOS*, length of hospital stay; *MACEs*, major adverse cardiovascular events.

**Table III.** Linearized rate of bleeding at follow-up

| | *C + OAT (n = 161) No of patients %/patient-year (95% CI)* | *C + ASA(n = 157) No of patients %/patient-year (95% CI)* | P *value* |
|---|---|---|---|
| Bleeding | 39 4.63 (3.89-5.37) | 24 2.99 ( 2.38-3.06) | .06 |
| Life-threatening/requiring hospitalization and/or transfusion | 15 1.78 (1.32-2.24) | 13 1.62 (1.17-2.07) | .7 |
| Not requiring hospitalization and/or transfusion | 24 2.85 (2.27-3.43) | 11 1.37 (0.95-1.78) | .03 |

*C + ASA*, Patients who underwent therapy with aspirin and clopidogrel; *C + OAT*, patients who underwent therapy with warfarin and clopidogrel.

the incidence of minor anticoagulation therapy-related complications, not requiring transfusion and/or hospitalization, was significantly higher in the C + OAT group than in the C + ASA group (2.85% patient-years vs 1.37% patient-years; $P = .03$). Patients with minor bleeding stopped their therapy for few days (generally not more than 1 week) and then restarted the same therapy: this subgroup of 35 patients (24 in C + OAT group and 11 in C + ASA group) did not show a significant difference in freedom of graft failure compared with all patient data: at 5-year follow-up, freedom of graft failure was 70.8% ± 2.7% (C + OAT) and 54.4% ± 3.9% (C + ASA), $P = .53$ and .56, respectively, vs all patient incidence.

At Kaplan-Meier analysis, the incidence of MACEs, including mortality, was found to be similar ($P = .34$) for both study groups (Fig 2), while the 3-, 5-, and 8-year overall graft patency rates were significantly higher in the C + OAT group compared with the C + ASA group (86.7% ± 2.7% vs 80.8% ± 3.2%; 77.3% ± 3.5% vs 63.3% ± 4.1%; 44.4% ± 7.2% vs 30.4% ± 5.9%, respectively; $P = .026$, Cox-Mantel test; Fig 3). Primary and primary-assisted graft patencies are depicted in Fig 4 for both treatment groups. Although the study was not conceived to analyze a prespecified subgroup of patients, the combination therapy shows the greatest difference in poor arterial runoff patients: at 5-year follow-up there was 56.1% ± 4.3% vs 29.7% ± 3.5% freedom from graft failure in the C + OAT and C + ASA groups, respectively ($P = .03$, OR = 3.0, 95% CI = 1.07-8.63), and at same follow-up time the graft patency rate for all patients was significantly higher than for poor runoff patients ($P = .01$ and .001, in the C + OAT and C + ASA groups, respectively). Long-term primary-assisted patency was obtained whenever possible by endovascular procedure (percutaneous transluminal angioplasty at the site of stenosis) or by bypass revision, when percutaneous transluminal angioplasty was not effective or technically suitable. The treatment (coumadin plus antiplatelet or double antiplatelet) was not changed.

The rate of freedom from severe peripheral arterial ischemia leading to amputation was significantly higher in C + OAT than in C + ASA patients (96.7% ±1.4% vs 92.2% ± 2.3%; 94.2% ± 2.0% vs 84.8% ± 3.1%; 77.6% ± 5.3% vs 63.9% ± 6.1%, respectively; $P = .044$, Cox-Mantel test; Fig 5).

With Cox analysis of any causes, age, preoperative ABPI, poor arterial runoff, urgent operation, and presence of diabetes were predictive of graft failure, while only age, urgent operation, and presence of diabetes were predictive of bleeding episode incidence (Table IV). The presence of an AK synthetic or of a BK vein graft did not influence the coprimary end points.

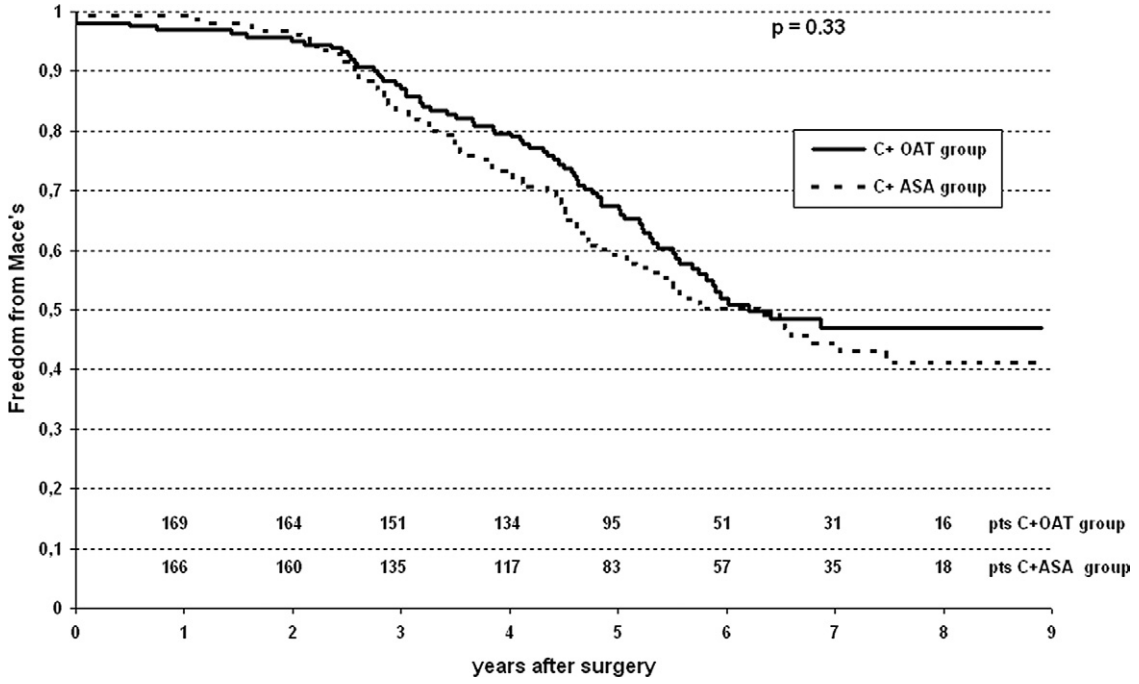


**Fig 2.** Freedom from graft failure for the two study groups. *C + ASA*, Clopidogrel plus acetylsalicylic acid therapy patients; *C + OAT*, clopidogrel plus oral anticoagulation therapy patients.

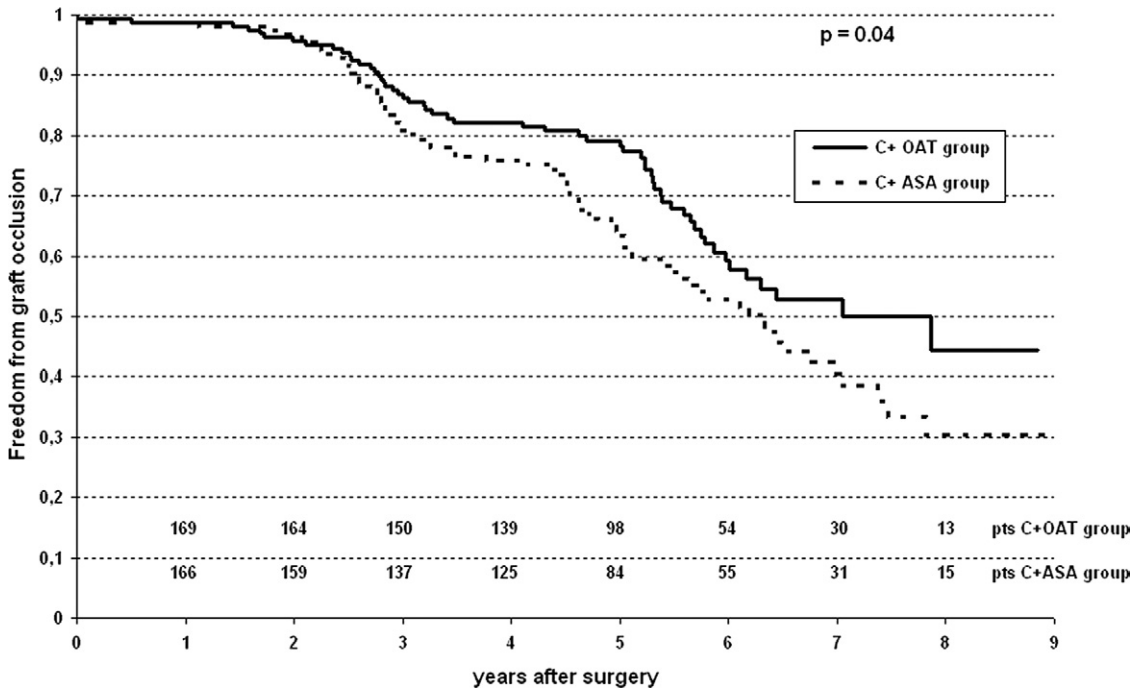


**Fig 3.** Freedom from major adverse cardiovascular events, including mortality, for the two study groups. *C + ASA*, Clopidogrel plus acetylsalicylic acid therapy patients; *C + OAT*, clopidogrel plus oral anticoagulation therapy patients.

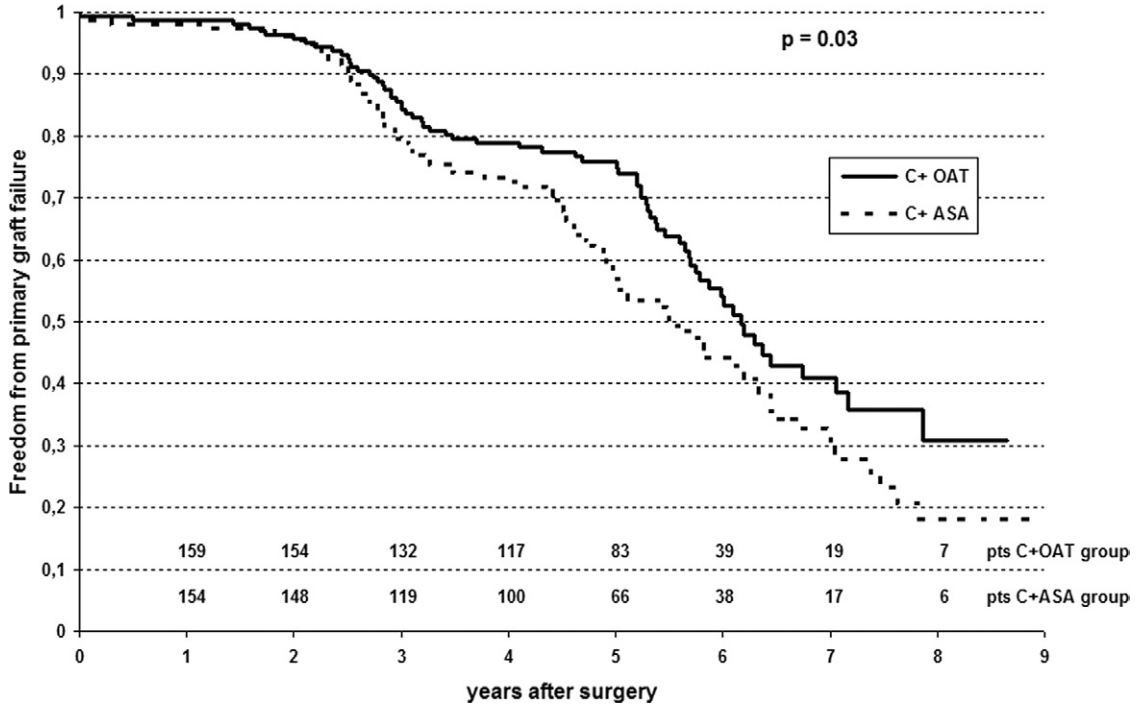


**Fig 4.** Freedom from primary graft failure for the two study groups. *C + ASA*, Clopidogrel plus acetylsalicylic acid therapy patients; *C + OAT*, clopidogrel plus oral anticoagulation therapy patients.

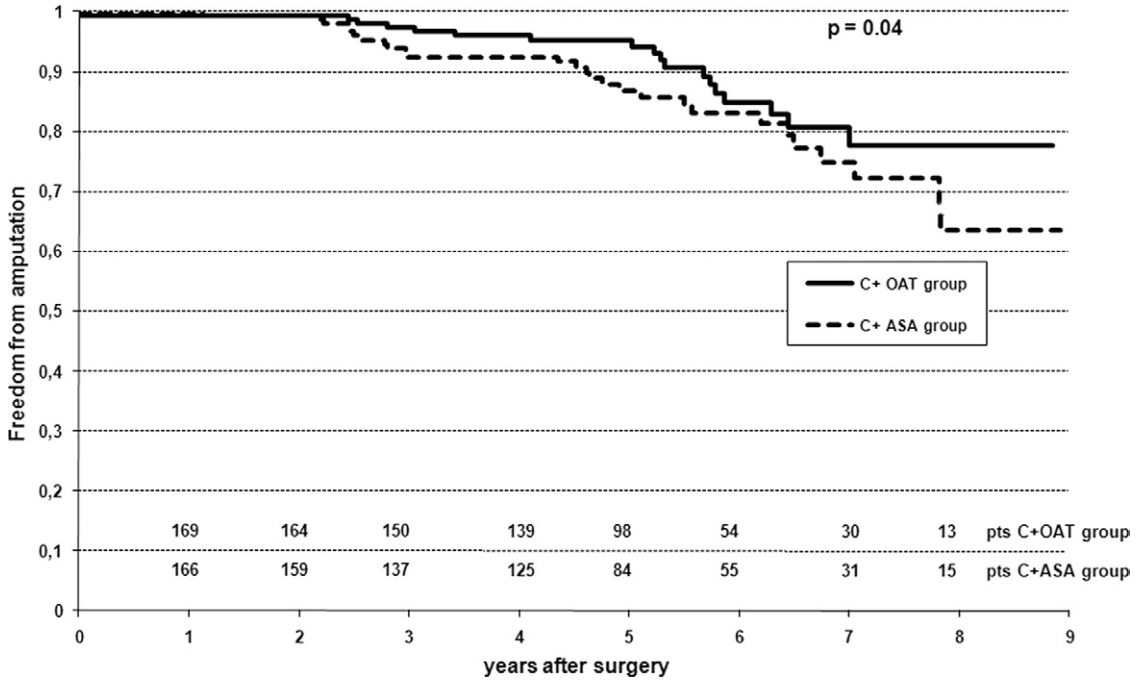


**Fig 5.** Freedom from amputation for the two study groups. *C + ASA*, Clopidogrel plus acetylsalicylic acid therapy patients; *C + OAT*, clopidogrel plus oral anticoagulation therapy patients.

**Table IV.** Cox hazards regression: independent predictors of long-term graft failure and of bleeding rate

| | *Graft failure* | | | *Bleeding rate* | | |
|---|---|---|---|---|---|---|
| *Predictors* | P *value* | *Exp (B)* | *95% CI* | P *value* | *Exp (B)* | *95% CI* |
| Age | .001 | 0.59 | 0.44-0.79 | .02 | 0.61 | 0.40-0.92 |
| Age$^2$ | .0006 | 0.35 | 0.23-0.68 | .001 | 2.98 | 1.68-5.27 |
| Urgent operation | .0001 | 2.87 | 1.81-4.55 | .005 | 0.09 | 0.01-0.58 |
| Preoperative ABPI | .0001 | 3.25 | 2.15-4.87 | .15 | 1.43 | 0.88-2.33 |
| Diabetes | .0001 | 2.42 | 1.58-3.78 | .01 | 1.65 | 1.11-2.64 |
| Poor arterial run-off | .0001 | 1.08 | 1.04-1.12 | .22 | 0.84 | 0.68-1.10 |

*ABPI*, Ankle-brachial pressure index.
All tested variables are listed in the text.

## DISCUSSION

The present study shows that, in patients who have undergone surgical femoropopliteal revascularization, clopidogrel plus warfarin combination therapy is more effective than dual antiplatelet therapy in increasing graft patency and in curbing the rate of severe limb ischemia requiring amputation. These beneficial effects are obtained with an increase in the rate of minor anticoagulation-related complications not requiring transfusion or hospitalization.

Our results compare favorably with previous studies in which long-term anticoagulation therapy with warfarin plus ASA in patients with arterial reconstruction for limb salvage improved the patency rate of femoropopliteal bypass graft.[16,29,30] Rosenthal, in a post hoc analysis, demonstrated that a subgroup of patients at high risk for graft failure was the one most likely to benefit from long-term anticoagulation therapy.[31] More recently, Jackson, in a multicenter randomized trial, demonstrated that combination therapy with warfarin plus ASA improved the patency rate only of prosthetic femoropopliteal bypass graft, but not of femoropopliteal vein grafts.[32]

The long-term anticoagulation therapy for patients with severe peripheral vascular disease is not without risk: the yearly cumulative incidence rate of hemorrhagic complications from long-term warfarin use ranges between 3% and 12%.[33] The Dutch Bypass Oral Anticoagulants or Aspirin Study showed an incidence of 2.9 hemorrhagic events per 100 patient-years.[34] The WAVE trial[15] has recently confirmed these results, reporting a 4% incidence of life-threatening bleeding in patients receiving a combination therapy (anticoagulant plus antiplatelet) compared with 1.2% in patients receiving antiplatelet therapy alone (RR 3.41; $P < .001$), while not preventing major cardiovascular complications. These findings are consistent with our data: while the incidence of MACEs, including mortality, on early and long-term outcomes was similar in the two study groups, we indeed found a significant improvement in peripheral arterial outcome at the expense of an increase in minor bleeding episodes. This difference could be explained by the use of clopidogrel as an antiplatelet drug and by the maintenance of a nonaggressive anticoagulation regimen (INR 2.0-2.5). Clopidogrel provides a substantial increase in quality-adjusted life expectancy for patients with either peripheral arterial disease or a recent stroke.[18,35-39] This favorable pharmacologic regimen, both in terms of efficacy and safety, may reduce the risks of a combination therapy with warfarin (at reduced dosage) and may improve peripheral arterial disease-related outcomes.

The anticoagulation intensity for the prevention of ischemic events in patients after femoropopliteal bypass graft surgery is usually obtained with an INR of 3.0 to 4.0.[33] Our results with a lower and narrower INR value range seem to be equally safe and effective in preventing such ischemic events.

Preoperative ABPI, despite the increasing sophistication of vascular surgical practice and its apparent simplicity, plays a key role in the assessment of symptomatic peripheral artery disease patients and in the management of therapeutic regimens.[40,41] In our patients, low preoperative ABPI did not influence early outcomes, while it was significantly associated with worse outcome at follow-up. The 30-day graft patency was higher, although not statistically significant, for C + OAT patients and only urgent operation, high risk for graft occlusion and hepatic dysfunction were significantly associated to coprimary end points.

We evaluated all patients in need of femoropopliteal bypass surgery and, despite the study design, we did not detect outcome differences between low- and high-risk patients; the presence of poor arterial runoff (about 25% of patients in our series) significantly influences graft occlusion rate, at early and long-term outcome. Moreover, to avoid a possible confounding factor, we excluded patients with renal function impairment requiring dialysis, a well-known risk factor for graft failure. Interestingly, in the Kaplan-Meier analysis, graft patency and limb salvage rates reach the highest difference between the two study groups around the 5- to 6-year follow-up and tend to maintain this difference up to the end of follow-up time. In these patients the combination therapy (C + OAT) seems to be most effective in the late years of follow-up, while in the first years of follow-up, it shows an efficacy comparable with that of dual antiplatelet therapy. This effect may be explained by age, which at multivariate analysis, negatively impacts long-term outcomes. In fact, we observed that the effect of age on survival is nonlinear, as documented by the inclusion of the square term in the model, showing that the worsening of peripheral arterial disease between ages 70

and 75 is much greater than that between ages 60 and 65. However, in spite of age effect, our results suggest that long-term anticoagulation therapy with warfarin and clopidogrel, besides improving graft patency rates, has also a favorable impact in preventing vascular events, by limiting the progressive occlusion of diseased arteries.

**Study limitations.** It could be useful to consider the quality of life outcomes, given the consistent risk of amputation in femoropopliteal bypass surgery patients and the need of having frequent blood tests for patients on anticoagulation therapy. The monitoring and hospitalization costs, also, were not determined, and this might be an important limitation of our study. Another limitation could be the lack of blinding of investigators, which is inherent in the trial design, and the lack of an independent event-adjudication committee. However, we believe that the open-label randomized study design, appropriately powered cohort, choice of end points such as graft patency, severe peripheral arterial ischemia, and incidence of bleeding episodes helps in minimizing this limitation.

**Implications.** Combination therapy of clopidogrel plus warfarin is more effective than dual antiplatelet therapy in increasing graft patency in patients with femoropopliteal arterial vascular surgery. This effect will not necessarily translate into better long-term secondary prevention of major cardiovascular events compared with antiplatelet therapy. The advantages of such a combination therapy may call for larger, multicenter trials to thoroughly investigate this important clinical issue.

## AUTHOR CONTRIBUTIONS

Analysis and interpretation: MM, LDT, PS
Data collection: GP, SL, VS
Writing the article: MM, PS, SL
Critical revision of the article: MM, LDT, PS, VS
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